Complete Summary

GUIDELINE TITLE

The use of chemotherapy and growth factors in older patients with newly diagnosed, advanced-stage, aggressive histology non-Hodgkin's lymphoma.

BIBLIOGRAPHIC SOURCE(S)

Hematology Disease Site Group. The use of chemotherapy and growth factors in older patients with newly diagnosed, advanced-stage, aggressive histology non-Hodgkin's lymphoma [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2003 Jun 25. 28 p. (Practice guideline; no. 6-7). [75 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Newly diagnosed, advanced-stage, aggressive histology non-Hodgkin's lymphoma

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Hematology
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To evaluate what treatment provides the optimum disease control and survival in older patients (at least 60 years of age) with newly diagnosed, advanced-stage, aggressive histology lymphoma
- To evaluate what toxicities are associated with these treatments
- To evaluate the role of granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) in combination with chemotherapy in these patients

TARGET POPULATION

Patients older than age 60 who have newly diagnosed, advanced-stage, aggressive histology non-Hodgkin's lymphoma, an Eastern Cooperative Oncology Group (ECOG) performance status of less than 4, and no significant comorbid illnesses

INTERVENTIONS AND PRACTICES CONSIDERED

1. Combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)
2. Other chemotherapy regimens, such as etoposide, mitoxantrone, and prednimustine (VMP); cyclophosphamide, pirarubicin, teniposide, and prednisone (CTVP); cyclophosphamide, teniposide, and prednisone (CVP), cyclophosphamide, mitoxantrone, vincristine, and prednisone (CNOP) (Refer to the original guideline document for a detailed listing of all of the chemotherapy regimens considered.)
3. Use of weekly fractionation schedule for delivery of chemotherapy
4. Addition of rituximab to cyclophosphamide, doxorubicin, vincristine, and prednisone
5. Use of granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF)

MAJOR OUTCOMES CONSIDERED

- Overall, progression-free, event-free, and relapse-free survival
- Toxicity
- Quality of life
- Response rates

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Searches were performed without language restriction in the following databases: PreMEDLINE & MEDLINE (1966 through January 2002, Week 2), CANCERLIT (1983 through October 2001), EMBASE (1980 to October 2001), Current Contents (1993 to October 2001), the Cochrane Library (Issue 4, 2001), Best Evidence (1991 to October 2001) and an unpublished theses database (UMI ProQuest®[40]). The following terms were used for MEDLINE and CANCERLIT: "lymphoma, non-Hodgkin" (Medical subject heading [MeSH], text word), "lymphoma" (text word) combined with "aged" (text word) or "older" (text word) combined with "chemo:" (text word). These terms were then combined with search terms for the following study designs: practice guidelines, systematic reviews, meta-analyses, and randomized controlled trials. The detailed search strategy has been described in Appendix I of the original guideline document.

Bibliographies of major textbooks, review articles, and primary studies were hand searched. Conference proceedings of the American Society of Hematology (1993-2001), American Society of Clinical Oncology (1993-2001), International (Lugano) Conference on Malignant Lymphoma (1996, 1999), and the European Cancer Conference (ECCO 1995, 1997, 1998, 2001) were searched. A manual review of the table of contents was performed for the following journals from 1993 to 1998: American Journal of Hematology, Annals of Oncology, Blood, British Journal of Hematology, Cancer, European Journal of Cancer, European Journal of Hematology, Journal of Clinical Oncology, and the New England Journal of Medicine. The Physician's Data Query (PDQ, National Cancer Institute, USA) clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) was searched for trials in progress using the terms "non-Hodgkin's lymphoma, adult" and "chemotherapy."

A separate search for studies assessing risk factors predictive of fever and neutropenia in elderly lymphoma patients was undertaken to assist the Hematology Disease Site Group (DSG) in evaluating the role of primary prophylaxis with growth factors. The following terms were searched in MEDLINE (1966 through September 2001) and CANCERLIT (1984 through September 2001): "lymphoma, non-Hodgkin" (MeSH, text word), "lymphoma" (text word) combined with "neutropenia" (text word) and "risk factor" (text word). Abstract publications were not included. Specific parameters to assess the quality of these studies were not applied.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were fully published reports or published abstracts of randomized controlled trials (RCTs) involving newly diagnosed patients with aggressive histology [intermediate- and high-grade, Working Formulation] lymphoma who were 60 years of age and older. The age threshold of 60 years was chosen in order to remain consistent with the findings of the International Prognostic Index (IPI).

1. To assess the role of chemotherapy, RCTs must compare at least two chemotherapy regimens.
2. To assess the role of colony-stimulating factors, RCTs comparing the use of granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) with a control group were sought. In the initial phase of this guideline, nonrandomized studies utilizing colony-

stimulating factors that included at least ten patients (chosen arbitrarily) were also eligible. These trials were subsequently made ineligible in February 2001 when data from three randomized trials became available.
3. Randomized studies assessing the use of monoclonal antibodies (e.g., rituximab) were eligible.
4. Subgroup analyses based on age or histology were eligible.

The outcome measures of interest included at least one of the following: overall survival (OS), disease-free (DFS) or failure-free survival (FFS), time-to-treatment failure (TTF), relapse-free survival (RFS), response rate, toxicity, or quality of life measures.

Exclusion Criteria

Studies were excluded if:

1. Patients included had indolent lymphoma, refractory or relapsed lymphoma, human immunodeficiency virus (HIV) related lymphoma, Hodgkin's disease, multiple myeloma, or other hematological malignancies;
2. Transplantation, maintenance chemotherapy, or interferon were used as interventions; or
3. Radiation therapy was used unevenly in experimental and control groups.

Studies assessing the role of chemotherapy were excluded if they incorporated growth factors as part of the primary therapy in all randomized groups. Also, letters and editorials were not considered.

Article Selection

Citations were blinded for authors, journal name, institution, and results by one author. An assessment was made by two independent observers who scored each blinded citation as: "yes" (inclusion criteria were met, no exclusion criteria were met); "no" (one or more exclusion criteria were met); or "maybe" (unclear from citation if article meets any criteria). The full-length article was retrieved if the citation scored "yes" or "maybe" by at least one observer. Inclusion and exclusion criteria were applied again to the full article if necessary. Interobserver kappa coefficients (quadratic weighted) were calculated using PCAgree© for the MEDLINE, CANCERLIT, and EMBASE databases, and an intraobserver coefficient was calculated from a random sample (random numbers table) of twenty MEDLINE citations for the citations assessing the role of chemotherapy. Acceptable kappa coefficients were 0.60 or greater. The citation lists for subsequent search updates were reviewed by one author using the same inclusion/exclusion criteria outlined previously.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)
Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Study Quality Assessment

Methodological assessment was performed using the published validated quality assessment tool of Jadad et al. for randomized controlled trials, but the score was not used to explicitly weight study results or to exclude studies from the analysis. This scale assigns one point if the study is randomized, one point if it is double-blinded, and another point if there is a complete description of withdrawals. An additional point each may be awarded if the randomization and the blinding were done appropriately. Studies may therefore score from zero to five points. It has been shown that studies scoring 2 points or less on this scale are more likely to produce treatment effects that are on average 35% larger than those produced by trials scoring 3 points or more. Randomized trials were also assessed based on whether the study population was explicitly defined, how baseline characteristics of the randomized groups compared, whether primary and secondary outcome measures and minimum important differences were stated, how the target sample size was projected, whether an intention-to-treat analysis was performed, whether randomization was concealed, whether co-interventions and endpoints were explicitly stated, and whether appropriate statistics were used.

Fully published articles are generally required in order to be most confident that the methodological assessment has identified the strengths and weaknesses of the trials. Most abstracts provide information of a more preliminary nature that may result in a lesser degree of confidence in making treatment recommendations. Subset analyses, while providing information of a hypothesis-generating nature, may be potentially misleading and thus provide limited information for devising treatment recommendations. Therefore, conclusions about the use of chemotherapy and growth factors are most influenced by the full paper publications of primary studies.

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Pooling trial results for both the chemotherapy and colony-stimulating factor trials was considered but was not feasible. The nature of the chemotherapy regimens tested was very heterogeneous, making meaningful results from pooling impossible. Pooling of outcomes for studies assessing granulocyte colony-stimulating factor (G-CSF) was also considered but was not feasible because of the differences in outcome measurement assessed and the timing of assessment. Where p values were missing in individual studies, the appropriate statistical test was done using the Statistical Package for the Social Sciences (version 8.0, SPSS Inc., Chicago, IL).

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The Hematology Disease Site Group (DSG) considered the management of older patients with aggressive histology lymphoma to be an important topic for guideline development because of its incidence, the availability of evidence, and a perception that practice patterns varied outside a range suggested by this evidence. The Hematology DSG concluded that treatment of these patients is complex, with the decision-making process requiring knowledge of available evidence and with application of this evidence to each patient after evaluating their specific circumstances, including their preferences. Based on the results of randomized trials that have tested many chemotherapy regimens founded on different principles, the Hematology DSG concluded that it is possible to provide specific treatment recommendations for older patients who have no significant comorbid health problems or specific preferences that would reduce the priority of providing therapy that offers the best opportunity of durable disease control.

The first topic dealt with the optimum base chemotherapy regimen. The Hematology DSG concluded that cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) should remain as standard therapy for these patients, just as it currently is for younger patients. The Hematology DSG concluded that age alone should not be the prime determinant for selecting the base chemotherapy regimen but that alternatives to CHOP should be reserved for patients of any age who have significant comorbid conditions or specific preferences. Physicians should be cautioned that many older patients might have significant comorbid illnesses or preferences that would make the use of CHOP inappropriate.

The second topic considered dealt with the addition of rituximab to CHOP. The Group d'Etude des Lymphomes de l'Adulte (GELA) trial testing this agent included patients ages 60 to 80 years with stage II-IV diffuse large B-cell lymphoma, an Eastern Cooperative Oncology Group (ECOG) performance status of less than 2 and no contraindications to doxorubicin. The Hematology DSG concluded that the reported data were sufficiently strong enough to justify a recommendation stating that these patients should receive rituximab in combination with CHOP. The Hematology DSG also discussed whether this recommendation should be generalized to other patients such as those older than 80 years, with limited stage disease, receiving chemotherapy other than CHOP, or receiving subsequent-line chemotherapy. The Hematology DSG concluded that patients older than 80 years who otherwise satisfy criteria for treatment with CHOP do not represent a specific prognostic entity and should, therefore, receive similar treatment to patients aged 60 to 80 years of age. The Hematology DSG concluded that current data are insufficient to support a recommendation to add rituximab to chemotherapy for patients with limited-stage or relapsed disease or for patients receiving chemotherapy other than CHOP.

The third topic considered dealt with the use of growth factors as part of primary therapy in combination with chemotherapy and rituximab. The Hematology DSG initially concluded that in the absence of trials detecting superior disease control, survival, or quality of life, current data were insufficient to support a recommendation to use growth factors as part of primary therapy. The

Hematology DSG did conclude that secondary prophylaxis with granulocyte colony-stimulating factor (G-CSF) was appropriate and recommended for patients who have experienced a previous episode of neutropenic fever or a treatment delay resulting from prolonged neutropenia. This initial recommendation concerning primary therapy did not achieve unanimous approval from the Hematology DSG—some members regarded a reduction in the risk of infection as a sufficient outcome to justify using granulocyte colony-stimulating factor as primary therapy for all patients. A minority of practitioners from across Ontario who reviewed the initial guideline (August 2000) also supported this position. With the availability of results from three randomized trials indicating that the absolute reduction in infections may be less than initially anticipated and with a review of data that assists in predicting which patients are at greatest risk of life-threatening infections, the Hematology DSG reached consensus for a modified recommendation. The Hematology DSG now concludes that there are insufficient data to support a recommendation to routinely use growth factors as part of primary therapy but does support the primary use of growth factors for patients at high risk of developing life-threatening infections. These patients are best identified as those with a poor (ECOG greater than 1) performance status. The Hematology DSG also concluded that this recommendation should be expanded to include those patients who present with neutropenia or who have an active infection at the time that therapy is commenced. The recommendation for using growth factors as part of secondary prophylaxis was not altered.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Practitioner feedback was obtained through a mailed survey of 110 practitioners in Ontario (49 medical oncologists, 30 hematologists, 21 pharmacists, and 10 resident hematologists). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. The practitioner feedback was mailed out on August 6, 2002 or October 28, 2002 for staff clinicians and October 10, 2002 for resident hematologists. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Hematology Disease Site Group (DSG) reviewed the results of the survey.

Practice Guidelines Coordinating Committee Approval Process

The practice guideline report was circulated to members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval at the May 2003 teleconference meeting. Twelve of 16 members of the PGCC attended the meeting, and all 12 approved the practice guideline report as written.

This practice guideline reflects the integration of the draft recommendations with feedback obtained from the external review process. It has been approved by the Hematology DSG and the Practice Guidelines Coordinating Committee.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- Combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) is recommended for patients with no apparent cardiac disease or significant comorbidity. Dose and schedule should be the same as that used in younger patients.
- The addition of rituximab to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) is recommended for patients with diffuse large B-cell lymphoma.
- There is insufficient evidence to support the routine use of granulocyte colony-stimulating factor as primary therapy.
    - While use of granulocyte colony-stimulating factor shortens the duration of neutropenia and decreases the infection rate in these patients, no differences in disease control or survival have been detected.
    - The primary use of granulocyte colony-stimulating factor is recommended for older patients who are at a particularly high risk of experiencing neutropenic fever. These patients are best identified as those with a poor performance status (Eastern Cooperative Oncology Group [ECOG] 2 or greater), neutropenia prior to therapy, or an ongoing infection; there are insufficient data to recommend the primary use of granulocyte colony-stimulating factor for patients whose sole risk factor is bone marrow involvement with lymphoma.
    - The use of granulocyte colony-stimulating factor as secondary prophylaxis is recommended for patients who have previously experienced an episode of neutropenic fever or a treatment delay resulting from persisting neutropenia.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

Including the updated searches, 23 publications (13 full papers, 10 abstracts) met the eligibility criteria for chemotherapy trials and were reviewed. Two systematic reviews were also found, one of which represents a portion of this document published as a systematic review.

Quality Assessment Scores

Of the 23 studies assessing the role of chemotherapy (see Table 2 in the original guideline document), three scored 3 on the Jadad quality scale, ten scored 2, and ten scored 1. The studies assessing the use of colony-stimulating factors scored 2 points and 1 point. One study assessing the role of rituximab scored 2 points.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- In a randomized trial comparing cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) with a regimen considered to be less toxic (etoposide, mitoxantrone, and prednimustine [VMP]), progression-free and overall survival were superior in the group receiving CHOP.
- In a randomized trial comparing a CHOP-like regimen, in which pirarubicin is substituted for doxorubicin and teniposide is substituted for vincristine (CTVP), with a regimen considered to be less toxic (cyclophosphamide, teniposide and prednisone [CVP]), progression-free and overall survival were superior in the group receiving CTVP.
- In a randomized trial comparing CHOP with a fractionated schedule of weekly CHOP, overall survival was superior in the group receiving standard CHOP.
- In two randomized trials comparing CHOP with a regimen in which mitoxantrone was substituted for doxorubicin (CNOP), progression-free and overall survival were superior in the groups receiving CHOP. In a third randomized trial in which a weekly doxorubicin-containing regimen was compared with a regimen in which mitoxantrone was substituted for doxorubicin, response rate and overall survival were superior in the group receiving the mitoxantrone-containing regimen. The investigators of this study are currently conducting a randomized trial in which the weekly mitoxantrone-containing regimen is compared with CHOP.
- In a randomized trial comparing CHOP to a combined regimen of rituximab and CHOP, event-free and overall survival were superior in the group receiving CHOP plus rituximab.
- In three randomized trials evaluating the primary use of granulocyte colony-stimulating factor, no differences between the randomized groups were detected in disease control or overall survival. Less severe granulocytopenia and fewer infections and days of antibiotic use were observed in patients receiving granulocyte colony-stimulating factor.

POTENTIAL HARMS

In three randomized trials evaluating the primary use of granulocyte colony-stimulating factor, less severe granulocytopenia and fewer infections and days of antibiotic use were observed in patients receiving granulocyte colony-stimulating factor.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Treatment decisions in older patients with aggressive histology lymphoma are complex and may be influenced by comorbidity, patient preferences, quality of life issues, and the goals of the treatment program. These factors may alter recommendations for individual patients and require discussion between health care providers, patients, and their families.
- Radiation therapy is not considered in this guideline and may be an important part of the treatment plan for these patients.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines is expected to use independent medical judgement in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Hematology Disease Site Group. The use of chemotherapy and growth factors in older patients with newly diagnosed, advanced-stage, aggressive histology non-Hodgkin's lymphoma [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2003 Jun 25. 28 p. (Practice guideline; no. 6-7). [75 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2003 Jun 25

GUIDELINE DEVELOPER(S)

Practice Guidelines Initiative - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario, Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Hematology Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Hematology Disease Site Group (DSG) disclosed potential conflict of interest information.

GUIDELINE STATUS

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline or Evidence Summary, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- The use of chemotherapy and growth factors in older patients with newly diagnosed, advanced-stage, aggressive histology non-Hodgkin's lymphoma

Summary. Toronto (ON): Cancer Care Ontario. Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on January 23, 2004. The information was verified by the guideline developer as of February 23, 2004.

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